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# Role of the Genetic Factors in the Development of Myopia

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## 1. Introduction

Myopia, also known as nearsightedness, is the most common eye disorder worldwide. In myopic peoples, the image of distant objects falls in front of the retina, either as the eye is too long (axial myopia), the cornea is too convex or the index of refraction of the lens is too high (refractive myopia). The light entering the eye is not focused correctly and distant objects look blurred [1]. The myopic eye is generally vulnerable and persons with  $\leq -6.0$  diopters (D) are more liable to a wide range of ocular pathologies. The development of high-grade myopia involves anterior-posterior enlargement of the eye, scleral thinning, changes in the diameter of scleral collagen fibrils, and frequent detachment of the retina resulting from stress related with axial elongation [2].

## 2. Epidemiology

The prevalence of myopia often varies with age, country, sex, race, ethnicity, occupation and environment [3]. In general, myopia firstly occurs in school-age children, and typically progresses until about the age of 21, because the eye continues to grow during childhood. However, myopia may also develop in adults due to visual stress or health conditions such as diabetes [4].

Myopia affects 25% people over age 40 in the Western Europe and the United States, making this condition the most common eye disorder in the West and constituting a significant public health and economic problem [5,6]. The cost of optical correction to provide clear distinct vision is considerable. Moreover, the development of high-grade myopia ( $\leq -6.0$  diopters [D]) [7] is a significant risk factor for other ocular diseases, including peripheral retinal and cho-

roidal degenerations, glaucoma, retinal detachment, premature cataracts, and finally blindness [8-10]. Consequently, great efforts have been undertaken to identify and understand the mechanisms underlying the development and progression of myopia. The estimated prevalence of high grade myopia is ~2.5 to 9.6% in the elderly world population [7,8]. However, its highest prevalence rates are in Asians, in whom almost 50 to 80% of the adult populations are myopic [10-12]. Recent population-based studies suggest that the prevalence is increasing, specifically in Asian populations. In some areas, such as China, India and Malaysia, up to 41% of the adult population is myopic to -1 diopters, up to 80% to -0.5 diopters. In some urban areas in East Asia, the prevalence of myopia among teenagers and young adults exceeds 70% [13]. A recent review observed that 26.6% of Western Europeans aged 40 or over have at least -1.0 diopters of myopia, and 4.5% have at least -5.0 diopters [7]. In China, myopia rate was the highest in the world: 400 million people are myopic out of its 1.3 billion people. The prevalence of myopia is 77.3% in high school students in China, and is more than 80% in college students. The prevalence of myopia has been reported as high as 70%-90% in some Asian countries, 30%-40% in Europe and the United States, and 10%-20% in Africa. By the year 2020, it is estimated that 2.5 billion people- 30% of the world's population- will be affected by myopia alone. Myopia is less common in the African population and associated diaspora. In American people between the age of 12 and 54, myopia has been observed to affect African Americans less than Caucasians. Asians had the highest prevalence followed by Hispanics. Caucasians had the lowest prevalence of myopia [7].

In addition, a number of studies have found that the incidence of myopia increases with level of education and many studies have shown a correlation between myopia and higher intelligence quotient (IQ), possibly due to the confounding factor of formal education [4].

### 3. Environmental and genetic factors in myopia

Myopia has a diverse etiology, with both environmental and genetic factors believed to be involved in the condition's development and progression. Whether myopia is due to inter-ethnic differences in the genetic predisposition to myopia or to culture-specific environmental influences remains uncertain.

The environmental factors implicated in myopia include near work, light exposure, lack of physical activity, diet, a higher level of education, and urbanization [14-17]. For instance, population-based studies have shown associations between myopia and higher socioeconomic status and greater levels of educational attainment [18]. High prevalences and progression rates of myopia have been reported in individuals in visually intensive occupations such as clinical microscopists, carpet weavers and visual display workers [19]. Within the context of the myopization process, education, socioeconomic status, and occupation are generally considered to be indirect surrogates for more proximal risk factors such as near-work visual demand. Studies of the effect of reading have attempted to show a more direct relationship between myopia and near work activity. Children with myopia spent more time studying, reading, and less time playing sports than children without myopia. Studies on

the effect of reading on the rate of progression of myopia have provided conflicting results. In the study of Singaporean school children, near work was not associated with worsening myopia [20]. On the other hand, myopic children in Finland who spent more time reading had faster rates of myopia progression [21]. The relationship between reading, near work activity and myopia is complex and still poorly understood. Assessment of exposure to near work is subject to considerable measurement error and is prone to bias in retrospective studies. Effect estimates may vary depending on the unit of measurement chosen (i.e. intensity, duration, reading distance or cumulative dose), outcome definitions (myopia, refractive error, rates of progression), or the ages, ethnicities and social circumstances. The current ubiquity of technologies such as computers, cellular and smart phones, and gaming devices has added a layer of complexity to the near work question. Indeed, it could be argued that the recent increase in myopia prevalence in East Asia reported in some studies may be the result of a steady rise in the use of modern electronic devices over the past three decades. Nevertheless, a direct link between the utilization of electronic devices and myopia development has yet to be convincingly established and future studies should attempt to validate and quantify this relationship [22].

While excessive reading or near work activity increase the risk of myopia, other environmental factors (such as playing sports and time spent outdoors) have shown protective relationships. Recent studies have shown that time spent outdoors and participation in outdoor sports during childhood is associated with a decreased risk of myopia [15]. Moreover, the beneficial effect of outdoor activity appears not to be the result of a concomitant reduction in near work. There is also evidence that genetic factors may interact with outdoor activity on the risk of myopia. The inverse relationship between outdoor activity and myopia development may be limited to children with a strong familial predisposition to myopia such as children with two myopic parents compared to children with either no, or one myopic parent.

While behavior and environment play important roles in refractive development, it has been convincingly established that heritable (presumably genetic) factors, are also important in ocular refraction. Familial aggregation studies have estimated sibling recurrence risks of common forms of refractive errors to range from 2 to 5.61 for myopia [23,24]. Moreover, children of myopic parents tend to have longer eyes and are more likely to develop myopia during childhood or adolescence. The strong familial effects for refraction phenotypes are present across populations with varying underlying distributions of refractive error. This observation is consistent with the hypothesis that environmental influences may drive regional and ethnic differences in refractive distribution, but that within-population variation is largely due to genetic factors.

However, HM is highly heritable and often appears as familial ocular disorder, where genetic predisposition seems to be a dominant factor of its development and progression [25-27]. Each type of Mendelian inheritance for familial HM has been described [28,29]. Myopia related genes include about 70 genetic loci to which primary myopias have been mapped, although the number is constantly increasing and depends to some extent on definition. Of these, several are associated with additional abnormalities, mostly as part of developmental

syndromes. These tend to result from mutations in genes encoding transcriptional activators, and most of these have been identified by sequencing candidate genes in patients with developmental syndromes [3].

To date, several genetic loci for nonsyndromic myopia (MYP) have been mapped, including 12 loci linked to HM: *MYP1*, chromosome Xq28, *MYP2* 18p11.31, *MYP3* 12q21-q23, *MYP4* 7q36, *MYP5* 17q21-q22, *MYP11* 4q22-q27, *MYP12* 2q37.1, *MYP13* Xq23-q25, *MYP15* 10q21.1, *MYP16* 5p15.33-p15.2 ; *MYP18* 14q22.1-q24.2, and *MYP19* 5p15.1-p13.3 [30-45]. Moreover, two recent independent genome-wide association studies involving large cohorts of refractive error patients identified loci at chromosome 15q14 and 15q25 [46,47].

Candidate gene association studies have revealed several HM susceptibility genes, including: collagen, type I, alpha 1 (*COL1A1*), transforming growth factor, beta 1 (*TGFB1*), transforming growth beta-induced factor (*TGIF*), lumican (*LUM*), hepatocyte growth factor (*HGF*), myocilin (*MYOC*), paired box 6 (*PAX6*), and uromodulin-like 1 (*UMODL1*) [48-62]. However, positive results have not been replicated, and inconsistent data have been published. Thus, the causative mutation(s) has not yet been found, suggesting genetic heterogeneity among studied populations.

A genetic association between the three single nucleotide polymorphism (SNP)s rs6214, rs10860860, and rs2946834 and familial myopia in a large, international cohort of myopia pedigrees of Caucasian origin, suggests that insulin-like growth factor 1 (*IGF-1*) may be a candidate gene for HM [63]. These three SNPs are located within the *MYP3* locus mapped to chromosomal region 12q21-q23. This locus was previously reported to be associated with autosomal dominant HM. The SNP rs6214 (reference allele G) lies in the 3'-untranslated region (UTR) of *IGF-1*, whereas the SNPs rs10860860 (reference allele A) and rs2946834 (reference allele C) are located in the noncoding sequence in close proximity to *IGF-1* [34,35].

The *IGF-1* gene encodes insulin-like growth factor (pIGF-1), which is a member of the signaling system involved in development, cellular growth, differentiation, protein translation, metabolism, apoptosis, and aging [64,65]. The association of *IGF-1* with numerous human diseases, such as diabetes, cancer, and growth failure has been reported. *IGF-1* has been also implicated in ocular diseases, including retinopathy of prematurity, age-related macular degeneration, and diabetic retinopathy [66-73]. The *IGF-1* gene polymorphisms investigations in Polish families do not support the studies reporting association of the SNPs rs 6214, rs10860860, and rs2946834 in the *IGF-1* gene with HM and any myopia phenotypes [74]. Haplotype analysis with informative crossovers in affected individuals defined a 12.2; 10.9; and 9.5 Mb genomic regions for high-grade myopia spanned between SNP markers rs11977885/rs10950639, rs11770622/rs9719399, and rs4763417/rs10842388 on chromosomes 7p22.1-7p21.1, 7p12.3-7p11.2, and 12p12.3-12p12.1 [75]. However, the polymorphism of rs12423791 in the Chinese population showed positive association with extreme myopia [76,77]. Further replication studies involving other populations are needed to investigate the possible role of *IGF-1* as a potential myopia candidate gene.

Quantitative analyses of 225 Caucasian families identified two additional potential loci at chromosome 6q13-16.1 and chromosome 5q35.1-35.2 for myopia [78].



#### 4. Preventive measures and treatment

Treatments that are currently available for slowing the progression of myopia include spectacle lenses, contact lenses, and pharmaceutical agents such as a non-selective muscarinic antagonist (Atropine). Several large studies conducted in different parts of the world have shown that the prevalence of myopia in children with more outdoor activity hours is lower than in children with fewer hours.

#### 5. Conclusion

Uncorrected refractive errors such as myopia and hyperopia are the most common causes of visual impairment worldwide. It is estimated that 2.5 billion people will be affected by myopia within the next decade. Epidemiological, experimental and clinical research has shown that refractive development is influenced by environmental and genetic factors for myopia. Genetic linkage studies have mapped the dozen loci, while association studies have found more than 70 different genes. Many of these genes are involved in common biological pathways known to mediate extracellular matrix composition and regulate connective tissue remodelling. Other associated genomic regions suggest novel mechanisms in the etiology of high myopia, such as mitochondrial-mediated cell death and photoreceptor-mediated visual signal transmission. The interactions between genes and environmental factors may be significant in determining individual risks of high myopia, and may help explain the pathogenetic mechanisms of myopia in human population.

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